REMARKS

Claims 15 and 17-35 are pending. Claim 15 has been amended to for clarity and spelling. No new matter has been added.

The specification has been amended to correct a typographical error. No new matter has been added.

Claim Objections

Claim 15 is objected to because of an incorrect claim identifier, which has been corrected herein.

Claims 15, 17-20, 22, 24, 26, 28 and 30-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Office Action page3)

The term "including" has been deleted thereby making this rejection moot.

Claims 15, 17-20, 22, 24, 26, 28, 30-35 were rejected under USC 103(a) as being unpatentable over Kimura et al. in view of Postma et al. (Office Action page 3)

The rejection can be logically rebutted by showing that the previously submitted data has been misinterpreted. Based on the empirical data in the Declaration, the invention now claimed in not obvious in light of the combination of references.

First Regarding Experiment 2 in the Declaration filed July 30, 2008, the rejection states that Applicant asserts that the data show that the commercial drug Theophylline does not treat Chronic Obstructive Pulmonary Disease (COPD) in patients. It is appears the applicants arguments have been misinterpreted, as the applicants assert that *Theophylline did not exhibit therapeutic effects at all*, while ***only compound No. 551 exhibits therapeutic effects***, based on the evaluation results of therapeutic effects of compound No. 551 (i.e. TA-270) and Theophylline against COPD model of a guinea pig induced by a cigarette smoke solution (CSS) and lipo-polysaccharide (LPS).

However, the applicants stated at page 10 of the response dated July 30, 2008 as follows:

> (W)ith regard to *airway resistance* that corresponds to FEVI in clinical evaluation, *both compound No. 551 and theophylline exhibited the same level of the improving effects*. However, *with regard to the increase in the residual volume that is characterized in COPD, the commercial drug "Theophylline" did not exhibit improving effects while compound No. 551 exhibits significant therapeutic effects in this pulmonary emphysema model.*

As above, Theophylline exhibits therapeutic effects to some extent in COPD model. The results are consistent with the reports of Zhou et al. cited in the rejection.

Two parameters for the respiratory function were evaluated in the Declaration. One is ***airway resistance*** and the other one is ***residual volume***.

Airway resistance in this experiment was evaluated by the respiratory resistance mainly due to contraction of central airway, and it is a parameter corresponding to FEVI in clinical practice. Thus, bronchodilator improves ***airway resistance***. Theophylline in this experiment exhibits a good improvement on ***airway resistance*** due to its bronchodilator activity (Fig. 3). To the contrary, although compound No. 551 has no bronchodilator activity, it exhibits an improvement on ***airway resistance*** to the same level with Theophylline (Fig. 3).

Residual volume is a parameter reflecting the function of lung parenchyma, not central airway. If an inflammation of lung parenchyma in COPD becomes worse, the contractile strength of lung gets weak. Then, the ***residual volume*** of lung, when air is exhaled, becomes large, and as a result the exchange rate of fresh air becomes lower. It has been reported that the ***residual volume*** increases in COPD patents of the clinical practice. The ***residual volume*** is a significant factor in COPD (see *previously submitted* Dykstra et al., Chest 1999, 115:68-74). It is described in Dykstra et al. as follows:

> Patents with moderate to severe airways obstruction and high ***residual volume*** (RV) and total lung capacity (TLC) levels were more likely to have COPD than asthma.(in the Abstract, Emphasis added)
>
> ...for patients with moderate to severe airways obstruction, ... the mean RV was higher in patients with COPD only when compared to patients with asthma only.... (in the paragraphs of 'Asthma vs. COPD' at page 71, col.1),

> ...in patents with moderate to severe airways obstruction, patients with COPD tend to have higher levels of RV and TLC when compared to patients with asthma. (at page 72, col.1).

Furthermore, in Experiment 2 of the Declaration, the positive control exhibited ***statistically significant increase of residual volume***, but ***Theophylline did not exhibit statistically significant improvement***. However, ***compound No. 551 decreased the residual volume with statistically significance***, and it ***was almost same level with normal control***. It means that ***compound No. 551 exhibits a significant improvement on the residual volume far exceeding the commercial drug Theophylline***.

It is not possible for a skilled person in the art to expect that compound No. 551 has an improved effect on the residual volume given that even Theophylline, which has been known as exhibiting a same level of an anti-inflammation effect as disclosed in Kimura et al., does not have. As such, ***compound No. 551 has unexpected therapeutic effects which are not obvious*** from the descriptions Kimura et al. and Postma et al.

Meanwhile, FEVI, quality of life (QOL) and exacerbation are evaluated in Zhou et al. cited in the rejection. Theophylline improves ***pre***-bronchodilators FEVI while it does not improve ***post***-bronchodilators FEVI. Therefore, it is consistent with the result that Theophylline exhibited an improvement on ***airway resistance*** in Experiment 2 in the Declaration.

As a result, claim 15 of the present invention and claims 17 to 35 depending on claim 1 are not *prima facie* obvious in light of the cited references which do not teach the same pathogenesis. Accordingly, it is respectfully requested that the rejection be reconsidered in light of this empirical evidence and withdrawn.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

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